REMARKS

Claims 1, 4-9, 52-55, 57, 59-66, 68-125 will be pending and under consideration upon entry of the above-made amendments. Claim 67 has been cancelled without prejudice. Claims 1, 53, 57, 66, 72 and 86 have been amended to clarify that which Applicants regard as the invention. New claims 87-125 have been added to more particularly claim a specific embodiment of the invention. The amendments to the claims and the new claims are fully supported by the specification as indicated below. No new matter has been added.

Claims 1, 53, 57 and 66 have been amended to recite that the lyophilate comprises an amphipathic lipid, a bioactive agent and a non-lipid surfactant. Accordingly, claim 67 which described a bioactive agent in the lyophilate has been cancelled without prejudice, and claims 72 and 86 have been amended to reflect the cancellation of claim 67.

Claim 53 has been amended to recite that the lyophilate upon reconstitution in aqueous solution results in a distribution of liposomes having a median diameter of less than 400 nm to clarify that the reconstitution itself results in such a distribution, without the need for any physical sizing methods. For the same reason, claim 66 has been amended to recite "wherein said lyophilate results in a distribution of liposomes in about one minute with hand-shaking upon addition of aqueous solution, said distribution of liposomes having a median diameter of less than 400 nm."

Claims 1 and 53 have been amended to correct typographical errors. In claim 1, the unit "μM" has been replaced by "μm." In claim 53, the spelling of the term, "amphipathic" has been corrected.

New claims 87-125 are similar to previous (i.e., prior to being amended) claims 1, 4-9, 52-55, 57 and 59-86; however, claims 87, 94, 97 and 105 recite that the composition which is lyophilized lacks halogenated solvent, and provides a lyophilate that upon reconstitution with aqueous solution, results in a distribution of liposomes that is suitable for administration to an animal. Furthermore, claims 87, 94, 97 and 105 expressly recite that the lyophilate (when reconstituted with aqueous solution) is "suitable for administration to an animal."

Support for the new claim recitations is found in the specification, for example, as set forth in the table below (citations being to the page and line numbers of the instant application).

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Claim No.	Support
87	Page 5, lines 13-20; page 10, lines 9-15; page 14, lines 3-8 and Example 1, pages 15-19.
88	Page 4, lines 5-7.
89	Page 7, lines 13-16.
90	Page 7, lines 17-19.
91	Page 4, line 7 through page 5, line 4.
92	Page 4, line 7 through page 5, line 4.
93	Page 4, line 7 through page 5, line 4.
94	Page 5, lines 13-20; page 10, lines 9-15; page 10, line 27 through page 11, line 2; page 14, lines 3-8 and Example 1, pages 15-19.
95	Page 4, lines 5-7.
96	Page 12, lines 1-18.
97	Page 5, lines 13-20; page 11, lines 14-16; page 14, lines 3-8; and page 10, lines 9-15; and Example 1, pages 15-19.
98	Page 4, lines 5-7.
99	Page 7, lines 13-16
100	Page 7, lines 17-19.
101	Page 12, lines 6-7.
102	Page 4, line 7 through page 5, line 4.
103	Page 4, line 7 through page 5, line 4.
104	Page 4, line 7 through page 5, line 4.
105	Page 5, lines 10-20; page 10, lines 9-15; page 11, lines 14-16; page 14, lines 3-8; and Example 1, pages 15-19.
106	Page 9, lines 5-8 and page 13, lines 6-12.
107	Page 4, lines 5-7.
108	Page 7, lines 13-16.

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109	Page 7, lines 17-19.
110	Page 12, lines 6-7.
111	Page 13, lines 6-12.
112	Page 13, lines 6-12.
113	Page 13, lines 6-12.
114	Page 13, lines 6-12.
115	Page 13, lines 6-12.
116	Page 13, lines 6-12.
117	Page 13, lines 6-12.
118	Page 13, lines 6-12.
119	Page 13, lines 6-12.
120	Page 13, lines 6-12.
121	Page 12, lines 6-7.
122	Page 4, line 7 through page 5, line 8.
123	Page 5, lines 10-12.
124	Page 32, lines 21-23.
125	Page 32, lines 21-23.

Rejections Under 35 U.S.C. § 103

Claims 1, 4-9, 52-55, 57 and 59-86 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 4,950,432 to Mehta et al. ("Mehta'432") or U.S. Patent-No. 5,811,119 to Mehta et al. ("Mehta'119"), further in view of U.S. Patent No. 5,585,112 to Unger ("Unger"), U.S. Patent No. 5,089,602 to Isliker ("Isliker"), or U.S. Patent No. 5,653,996 to Hsu et al ("Hsu"), individually or in combination.

In particular, the Examiner notes that Mehta '432 teaches preliposomal powder having a drug and phospholipid mixture. The Examiner contends that the reference discloses a preparation that involves dissolution of the lipid in a mixture of t-butanol-water, and lyophilization of the resulting mixture into a pre-liposomal powder. The Examiner notes that the reference teaches that liposomes could be produced by incubation and suspension in an aqueous solution. Similarly, the Examiner contends that Mehta '119 teaches a method of preparing a preliposomal powder by dissolving the lipids in a t-butanol-water mixture,

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followed by lyophilization of the mixture. It is said that liposomes could be produced from the powder by incubation and suspension in aqueous solution. The Examiner concedes, however, that the Mehta references fail to disclose the use of surfactants, e.g., Tweens, in the preliposomal preparations.

The Examiner relies on Unger, Isliker, and Hsu for the teaching of the use of Tweens in liposomal preparations. The Examiner argues that the use of Tweens in the preparations of Mehta would have been obvious to one of ordinary skill in the art since Tweens are routinely used in liposomal preparations. Specifically, the Examiner notes that Unger discloses non-ionic detergents such as Tweens to stabilize the liposome compositions.

Applicants respectfully disagree with the Examiner's rejection. To establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the claim limitations. *M.P.E.P. 2143.* Here, the cited references fail to teach or suggest a solvent that comprises t-butanol and water from which the claimed lyophilate is formed as required by claims 1, 53, 57 and 66. In particular, an inspection of the passages cited by the Examiner that allegedly disclose a t-butanol-water solvent in Mehta'432 (abstract, columns 5-7) and Mehta'119 (abstract and Example 1), and the entire texts of the references, reveals that both references are silent in describing a solvent containing t-butanol and water. Rather, both Mehta references describe lipid solutions in t-butanol alone. For example, Mehta '432 describes a "fourth solution" formed by dissolving a remnant (concentrate of polyene macrolide and phospholipid) in a solvent "consisting essentially of tertiary butanol" (see, abstract, col. 6, lines 20-25). Furthermore, Applicants note that Unger, Isliker, or Hsu fail to specifically teach or suggest a solution containing t-butanol and water from which the claimed lyophilate is formed. The aqueous/t-butanol solvent system provides the claimed invention with advantages over t-butanol alone. For instance, among other things, the aqueous/t-butanol solvent system should provide increased solubility for some bioactive agents when compared with solvent systems containing only t-butanol. Additionally, the physical characteristics of the lyophilate formed upon lyophilization of the claimed aqueous/t-butanol system may be different from those of lyophilate formed from a purely aqueous system due to the presence of the organic compound (*See* Kasraian et al. *Pharmaceutical Research* 12: 484-490 (1995)).

Accordingly, absent a description or suggestion of the aqueous/t-butanol solvent system as specified by the claimed invention, the rejection cannot stand.

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Second, the cited references are silent with respect to the property that the pre-liposomal lyophilates, upon reconstitution with aqueous solution, result in a distribution of liposomes having a median diameter of less than 1 μm, as specified by claim 1; or less than 400 nm, as specified by claims 53, 57 and 66. Among other things, this property renders the claimed compositions useful as reconstitutable formulations for preparation in a hospital pharmacy just prior to administration. See instant specification at p. 13, line 28 through page 14, line 2. Further physical sizing (e.g., extrusion, sonication) of the liposomes is unnecessary to achieve a distribution of liposomes having a median diameter of less than 1 μm (or less than 400 nm). Applicants note that the recitation of "upon reconstitution with aqueous solution, results in a distribution of liposomes having a median diameter of less than 1 μm" would clearly indicate to the skilled artisan that such is the direct result of reconstitution, thereby obviating the need for physical sizing steps. (This recitation also renders unnecessary the Examiner's suggested amendment to the claims to recite "consisting essentially of.")

In particular, Mehta '432 and Mehta '119, which fail to teach the inclusion of surfactants in the disclosed liposomal compositions, do not teach forming submicron-sized liposomes upon incubation and suspension of the lyophilates with aqueous solution. Indeed, in the exemplified liposomal composition in Mehta'119, the liposomes were all observed to be larger than 1 micrometer (col. 8, lines 18-21).

Unger fails to describe a distribution of liposomes that have a median diameter of less than 1 micrometer that results upon reconstitution of a lyophilate. Instead, Unger describes adjusting the size of the liposomes using procedures known to those of skill in the art, e.g., filtration, sonication, homogenization, etc. See col. 26, lines 31-57 of Unger. Moreover, a review of Example 10 of Unger shows that the liposomes formed by the disclosed procedure (which includes sodium lauryl sulfate as a liposomal component and includes a lyophilization step) produces liposomes having an average size range of 15 to 45 μm (with 1 mol% sodium lauryl sulfate) and 15 to 35 μm (with 10 mol% sodium lauryl sulfate). The sizes of these liposome are clearly outside the size of the liposomes formed upon reconstitution of the instantly claimed lyophilates.

Similarly, Isliker fails to specifically describe a distribution of liposomes that has a median diameter of less than 1 micrometer that results upon reconstitution of a lyophilate. Furthermore, while Isliker discloses the use of surfactants for the deaggregation

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or solubilization of lipoprotein aggregates during purification (col. 3, lines 28-34; col. 4, lines 58-64), Isliker neither teaches nor suggests a lyophilate which contains surfactant at the time of lyophilization. Moreover, Isliker teaches the removal of surfactant prior to lyophilization (see col. 4, lines 61-64 and col. 8, lines 47-51). Therefore, Isliker teaches neither a lyophilate which results in a distribution of liposomes at the time of reconstitution with a median diameter of less than 1 micrometer, nor a lyophilate which even contains surfactant.

Finally, Applicants point out that Hsu is improperly combined with Mehta'432 or Mehta'119 (optionally in combination with the other references cited by the Examiner), since the teachings of Hsu and Mehta ('432 or '119) fail to suggest the desirability of the proposed combination. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is a suggestion found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *M.P.E.P. 2143.01*. Hsu discloses methods for the preparation of liposomes utilizing the aerosolization of a solution comprising bilayer forming material and optional additional molecules onto an aqueous surface. While Hsu teaches the use of surfactants as a component of the bilayer forming materials, it does not teach or suggest forming a lyophilate that lacks liposomes as described in the instantly claimed lyophilates. Instead, Hsu describes preparation of lyophilates following liposome formation using the aerolization process (see, for example, col. 12, lines 37-58; and col. 17, lines 3-22). In the exemplified lyophilization procedure, the vehicle for the liposome concentrate from which the which the lyophilate is formed is largely aqueous buffer (see col. 17, lines 1-22).

In contrast to Hsu, the Mehta references describe a process where a solution of phospholipids and drug (i.e., polyene macrolide, caretenoids) in an organic solvent (see col. 7, lines 14-16 of Mehta '119) or more specifically, tertiary butanol is frozen, and then lyophilized to form a stable powder. Moreover, as noted, *supra*, Mehta'432 describes lyophilization of a frozen solution formed from dissolving a remnant (concentrate of polyene macrolide and phospholipid) "consisting essentially of tertiary butanol" (see, abstract, col. 6, lines 20-25). From either reference, one of ordinary skill in the art would fail to recognize any reason to substitute the organic solvent as described in Mehta for the aqueous solvent described in Hsu to prepare the desired stable liposomal composition upon lyophilization of the frozen composition. Accordingly, absent any motivation to combine the references, Applicants submit the proposed combination of Hsu with Mehta'432 and/or Mehta'119 is

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improper.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 4-9, 52-55, 57 and 59-86 under 35 U.S.C. § 103(a).

Claims 1, 4-9, 52-55, 57 and 59-86 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 4,950,432 to Mehta et al. ("Mehta '432") or U.S. Patent No. 5,811,119 to Mehta et al. ("Mehta '119"), further in view of JP 06-227966 ("JP 227966"), JP 06-183953 ("JP 183953") individually or in combination.

In particular, the Examiner notes that Mehta '432 teaches preliposomal powder having a drug and phospholipid mixture. The Examiner contends that the reference discloses a preparation that involves dissolution of the lipid in a mixture of t-butanol-water, and lyophilization of the resulting mixture into a pre-liposomal powder. The Examiner notes that the reference teaches that liposomes could be produced by incubation and suspension in an aqueous solution. Similarly, the Examiner contends that Mehta '119 teaches a method of preparing a preliposomal powder by dissolving the lipids in a t-butanol-water mixture, followed by lyophilization of the mixture. The Examiner asserts that liposomes could be produced from the powder by incubation and suspension in an aqueous solution. The Examiner concedes, however, that the Mehta references fail to disclose the use of surfactants, e.g., Tweens, in the preliposomal preparations.

The Examiner relies on JP 227966 and JP 183953 for the teaching of the inclusion of non-ionic surfactants, e.g. Tweens, in the preliposomal preparations. In particular, the Examiner notes that JP 227966 teaches the inclusion of a nonionic surfactant to form temperature-sensitive liposomes which are stable for a long time. Furthermore, the Examiner notes that JP 183953 teaches the inclusion of a nonionic surfactant to produce uniform size liposomes. The Examiner reasons that it would have been obvious to those of ordinary skill in the art to include nonionic surfactants in the preliposomal lyophilizates of Mehta to make the liposomes temperature-sensitive as disclosed by JP 227966, or to produce liposomes of a uniform size as disclosed by JP 183953.

Applicants respectfully disagree with the Examiner's rejection. The rejection should be withdrawn because the references fail to teach or suggest all of the limitations of the rejected claims. As noted, *supra*, both Mehta references fail to describe a solvent containing t-butanol and water from which the lypophilate is formed as required by the

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claimed invention. Rather, both Mehta references describe lipid solutions in t-butanol alone. JP 227966 and JP 183953 fail to remedy this deficiency as both references are silent as to using lyophilization methods to prepare liposomes.

Furthermore, the cited references are silent with respect to the property that the preliposomal lyophilates, upon reconstitution with aqueous solution, result in a distribution of liposomes having a median diameter of less than 1 µm, as specified by claim 1; or less than 400 nm, as specified by claims 53, 57 and 66. Among other things, this property allows the claimed compositions to be particularly useful as reconstitutable formulations for preparation in a hospital pharmacy just prior to administration. See instant specification at p. 13, line 28 through page 14, line 2. Further physical sizing (e.g., extrusion, sonication) of the liposomes is unnecessary to achieve a distribution of liposomes having a median diameter of less than 1 µm (or less than 400 nm). Applicants note that the recitation of "upon reconstitution with aqueous solution, results in a distribution of liposomes having a median diameter of less than 1 µm" would clearly indicate to the skilled artisan that such is the direct result of reconstitution, thereby obviating the need for physical sizing steps.

The Mehta references, as noted above, fail to teach the inclusion of surfactants in the disclosed liposomal compositions, and are silent with respect to forming submicron-sized liposomes upon incubation and suspension of the lyophilates with aqueous solution. JP-183953, while disclosing lipid membrane vesicles of 100-3000 Å particles, fails to teach or suggest that submicron-sized liposomes can be formed in the absence of further physical-sizing methods. Instead, JP 183953 teaches use of ultrasonication, a known liposome sizing technique, to achieve the disclosed liposome membrane vesicles. See, paragraphs 9 and 12. Moreover, JP 227966 fails to remedy this deficiency as it is silent with respect to the sizes of the liposomes formed. Therefore, Applicants submit that the cited combination fails to teach or suggest all the claim limitations.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1, 4-9, 52-55, 57 and 59-86 under 35 U.S.C. § 103(a).

New claims 87-125 have been added to more particularly claim a specific embodiment of the invention. Applicants submit that the invention as defined by the new claims is patentable in view of the cited references and, in particular, in view of U.S. Patent No. 4,950,432 to Mehta et al. ("Mehta '432") and U.S. Patent No. 5,811,119 to Mehta et al. ("Mehta '119"). The new claims specify lyophilizing a composition that lacks halogenated

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solvent, and that the distribution of liposomes which results therefrom upon reconstitution is suitable for administration to an animal. As will be apparent to skilled artisans, the presence of residual halogenated solvents in compositions (e.g., from preparation of the compositions) may pose unacceptable toxicity risks when the compositions are administered to animals (including humans). For instance, as described in Nitschke et al. *Fundamental & Applied Toxicology* 11: 48-59 (1988); exposure to methylene chloride resulted in an increased incidence of mammary tumors and multi-nucleated hepatocytes in rats.

In spite of this disadvantage of using methylene chloride, Mehta'432 specifically describes dissolving a residue containing a polyene macrolide and phospholipids in a mixture of tertiary butanol and methylene chloride as a step in the pre-liposomal powder formation. See column 6, lines 15-20. Moreover, a preferred solvent used in forming the residue is chloroform. See column 6, lines 1-15. Thus Mehta'432 does not suggest lyophilizing a composition that lacks halogenated solvents, while the other reference, Mehta'119, does not teach liposomes of submicron distribution. Accordingly, the invention defined by the new claims is not taught or suggested by either of the Mehta references, alone or in combination with the other references cited by the Examiner.

CONCLUSION

Applicants respectfully request that the present amendment and remarks be entered and made of record in the instant application. It is submitted that all the outstanding rejections have been obviated or overcome. An allowance of the application is earnestly requested. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Respectfully submitted,

Date: 1-24-05

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Enclosures

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